Available online at www.sciencedirect.com
ScienceDirect
Mathematical Biosciences xxx (2007) xxx–xxx
Mathematical Biosciences
www.elsevier.com/locate/mbs

Estimation of the reproduction number of dengue fever from spatial epidemic data ☆

G. Chowell [a,*], P. Diaz-Dueñas [c], J.C. Miller [a], A. Alcazar-Velazco [c], J.M. Hyman [a], P.W. Fenimore [b], C. Castillo-Chavez [d]

[a] *Center for Nonlinear Studies & Mathematical modeling and Analysis Group (MS B284), Los Alamos National Laboratory, Los Alamos, NM 87545, USA*
[b] *Theoretical Biology and Biophysics Group (MS K710), Los Alamos National Laboratory, Los Alamos, NM 87545, USA*
[c] *Instituto Mexicano del Seguro Social (IMSS), Colima, Col. 28010, Mexico*
[d] *Department of Mathematics and Statistics, Arizona State University, P.O. Box 871804, Tempe, AZ 85287-1804, USA*

Received 19 May 2006; received in revised form 14 November 2006; accepted 28 November 2006

Abstract

Dengue, a vector-borne disease, thrives in tropical and subtropical regions worldwide. A retrospective analysis of the 2002 dengue epidemic in Colima located on the Mexican central Pacific coast is carried out. We estimate the reproduction number from spatial epidemic data at the level of municipalities using two different methods: (1) Using a standard dengue epidemic model and assuming pure exponential initial epidemic growth and (2) Fitting a more realistic epidemic model to the initial phase of the dengue epidemic curve. Using Method I, we estimate an overall mean reproduction number of 3.09 (95% CI: 2.34, 3.84) as well as local reproduction numbers whose values range from 1.24 (1.15, 1.33) to 4.22 (2.90, 5.54). Using Method II, the overall mean reproduction number is estimated to be 2.0 (1.75, 2.23) and local reproduction numbers ranging from 0.49 (0.0, 1.0) to 3.30 (1.63, 4.97). Method I systematically overestimates the reproduction number relative to the refined Method II, and hence it would overestimate the intensity of interventions required for containment. Moreover, optimal intervention with defined resources demands different levels of locally tailored mitigation. Local epidemic peaks occur between the 24th and 35th week of the year,

☆ Los Alamos Unlimited Release LA-UR-06-3573.

* Corresponding author. Tel.: +1 505 665 9176; fax: +1 505 665 5757.
E-mail address: chowell@lanl.gov (G. Chowell).

0025-5564/$ - see front matter Published by Elsevier Inc.
doi:10.1016/j.mbs.2006.11.011

and correlate positively with the final local epidemic sizes ($\rho = 0.92$, P-value < 0.001). Moreover, final local epidemic sizes are found to be linearly related to the local population size (P-value < 0.001). This observation supports a roughly constant number of female mosquitoes per person across urban and rural regions. Published by Elsevier Inc.

Keywords: Dengue; Dengue hemorrhagic fever; Spatial epidemic data; Mathematical model; Stage progression; Reproduction number; Colima; Mexico

1. Introduction

Dengue, a mosquito-borne disease, is endemic in many countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific. It is a major public health problem in tropical and subtropical regions around the world (see the recent situation in Singapore [38]). The etiological agent is a flavivirus with four different serotypes. Individuals who recover from one serotype become permanently immune to it but may become partially immune, temporarily immune, or both to other serotypes [44]. The presence of dengue antibodies to a different serotype is an important correlate of severe disease. The World Health Organization estimates 50 million annual, worldwide cases of dengue [44].

We estimate the transmissibility of dengue fever during the 2002 dengue epidemic in the Mexican state of Colima using two different methods and municipal epidemic data to evaluate the effect of spatial heterogeneity [48,21]. The first method uses a standard dengue epidemic model (with fixed incubation periods in both hosts and vectors and an exponentially distributed infectious period in hosts) and assumes pure initial exponential epidemic growth to estimate the reproduction number. The second approach uses an epidemic model that incorporates more realistic incubation and infectious period distributions and estimates the reproduction number via trajectory matching to case notification data. We explore the relationships between the onset, peak, and size of local dengue epidemics as well as the correlation between local final epidemic and local population size.

For directly transmitted infectious diseases, the *basic reproduction number* ($\mathcal{R}_0$) is defined as the number of secondary cases generated by a primary infectious case during its period of infectiousness in an entirely susceptible population at a demographic steady state [1,14,15,3]. For vector borne diseases, $\mathcal{R}_0$ is the number of secondary cases generated by a primary infectious case via the vectors in an entirely susceptible population. Typically, if $\mathcal{R}_0 > 1$ an epidemic occurs while if $\mathcal{R}_0 < 1$ no outbreak is likely. $\mathcal{R}_0$ is used to quantify the intensity of control interventions necessary to contain an outbreak. In the case of malaria, Sir Ronald Ross [46] introduced a mathematical model with the purposes of showing that malaria can be greatly reduced by lowering the mosquito population density below a certain threshold.

In the case of recurrent infectious diseases such as dengue, *the reproduction number* $\mathcal{R}_p$ accounts for residual immunity generated by prior exposures to dengue in the population. We model $\mathcal{R}_p = (1-p)\mathcal{R}_0$ where p is the proportion of the population that is effectively protected at the beginning of the outbreak. Background immunity (in the population) depends on several factors including the (ordered) history of circulating dengue strains, birth rates, natural deaths and migration, and the epidemiology of the invading strain. For example, individuals who recover from a dengue serotype do so with permanent immunity to that serotype. This strain-specific immune

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

response may also provide partial and/or temporary protection against other serotypes [44], even though cross-reactive, but non-neutralizing, antibodies are an important causative factor of dengue hemorrhagic fever, a severe form of dengue disease [49]. Population models of interacting dengue strains have been theoretically explored (see for example [22,19,12,51]). Reliable estimates of $\mathcal{R}_p$ would help get useful ''bounds'' on control measures, that is, on measures that would make $\mathcal{R}_p < 1$. The estimation of the basic reproduction number $\mathcal{R}_0$ is not possible because it would require data on the immunological history of the population from prior exposure to the dengue strains. Here we estimate the reproduction number $\mathcal{R}_p$ (often denoted by $\mathcal{R}$).

Estimates of the reproduction number of dengue fever vary considerably between studies [31,36,37,20,23]. The reasons behind the variability on the estimates are not well understood. It may be due to the severity of the dengue serotype under consideration, the quality of public health surveillance, and/or local climatological conditions that affect vector numbers. Methods for estimating the reproduction number use data on the intrinsic growth rate of the epidemic [36,37,20]; on the relation between the reproduction number and the final epidemic size [31]; and age-stratified sero-prevalence surveys [23]. We evaluate the effects of assuming fixed incubation periods, an exponentially distributed infectious period in hosts, and exponential initial epidemic growth in the estimation of the reproduction number.

2. Materials and methods

2.1. Background

Dengue is transmitted in urban and semi-urban areas by its principle mosquito vector *Aedes aegypti*. *A. aegypti* is a highly anthropophilic daytime feeder, living around densely populated human habitats. Most significant for human disease are females that lay eggs in containers of standing water. Humans are infected when bitten by feeding infectious females. Susceptible mosquitoes acquire the infection when feeding on infectious humans.

Different aspects of the transmission dynamics of dengue are known to depend on climatological conditions; those aspects include the survival and development of the vector *A. aegypti* [30,32,39]. The extrinsic incubation period and the susceptibility of the mosquito have been observed to depend on temperature [39]. Seasonal variations in temperature and rainfall have been observed to be correlated with levels of dengue infection, with a higher number of dengue cases associated with higher rainfall and temperature, probably because of the resulting increases in mosquito breeding sites [31,47,10].

Cases of dengue range from asymptomatic [49] to clinically non-specific flu-like symptoms to dengue fever (DF) to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue hemorrhagic fever and dengue shock syndrome are the most severe forms of dengue disease. Many primary dengue infections are asymptomatic. DHF and DSS have been observed with secondary dengue infections beginning at age one and with primary infections in infants born to dengue-immune mothers [49,27]. Dengue attack rates vary from 40% to 50% but may reach 80% to 90%. The case fatality rate of dengue hemorrhagic fever can exceed 20% in the absence of treatment but it may be reduced to less than 1% with appropriate medical therapy [44].

Mexico was free of both dengue and the principal vector *A. aegypti* in the early 1960s but *A. aegypti* reinvaded Mexico in 1978 [31]. At least three dengue serotypes have co-circulated in

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

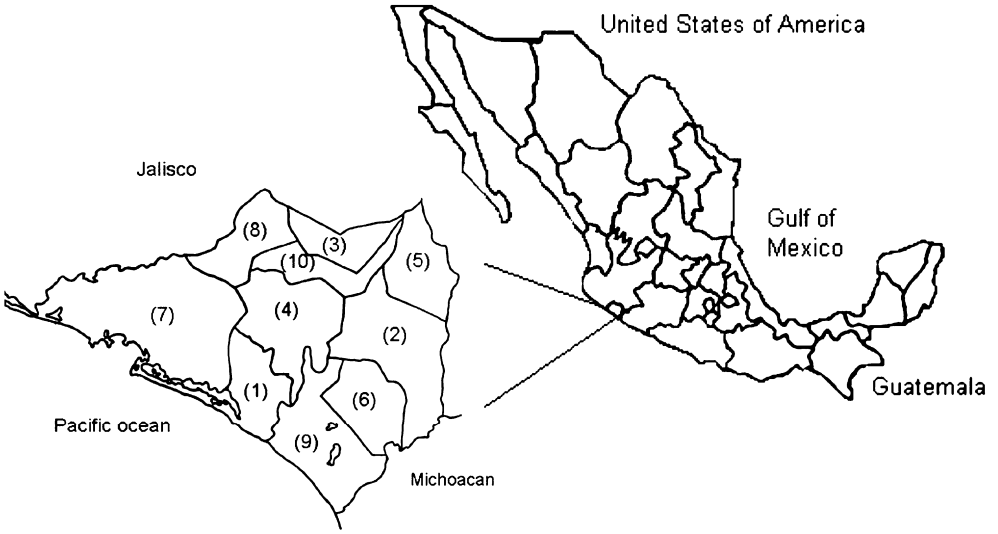

Fig. 1. Map of Mexico highlighting state boundaries. The state of Colima is located on the central Pacific coast. It has a tropical climate, a surface of 5455 km^2, a coastline extending 157 km, and a population of approximately 488,028 inhabitants [13]. The state of Colima is divided in 10 municipalities: Armeria (1), Colima (2), Comala (3), Coquimatlan (4), Cuauhtemoc (5), Ixtlahuacan (6), Manzanillo (7), Minatitlan (8), Tecoman (9), and Villa de Alvarez (10).

Mexico since 1983 [33], and DHF has become a public health problem in Mexico in 1994 [41]. The delay in the appearance of DHF after the reintroduction of the dengue virus is presumably the consequence of the strong correlation between non-neutralizing antibodies and severe disease. In some regions, annual epidemics of dengue have been observed, while in others, only sporadic epidemics have taken place. The latter is the situation in Colima, Mexico, located on the central Pacific coast (Fig. 1), where *A. aegypti* is endemic [17]. Colima has a tropical climate with a mean temperature of 23.2 °C, an area of 5455 km^2, a coastline extending 157 km, and a population of approximately 488,028 inhabitants (89 inhabitants/km^2) [13]. More than one serotype is co-circulating in the population [18,25]. The state of Colima is divided into 10 municipalities (Fig. 1). The 1997 dengue epidemic in Colima [18] was followed by the 2002 outbreak we study in this paper. 2002 was a year of high dengue incidence worldwide. Over 30 Latin American countries reported a total of over a million cases of classical dengue and more than 17,000 cases of dengue hemorrhagic fever [27].

Several explanations have been proposed to explain the re-emergence of dengue in regions where it had been absent for prolonged periods of time. Reasons for re-emergence include the immigration of people infected with absent strains which naturally brought reductions in mean herd immunity. In Colima, only sporadic epidemics of dengue have been documented. However, continuous low levels of transmission often go undetected by standard (low intensity) public health surveillance [17].

2.2. Data sources

We use the weekly number of dengue cases diagnosed in the hospitals of the Mexican Institute of Public Health (IMSS) during the 2002 Serotype-2 epidemic in the state of Colima. The IMSS

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

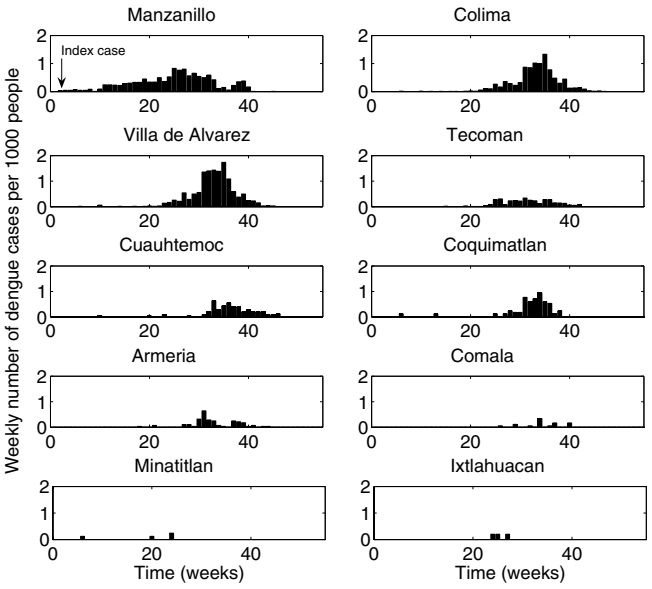

Fig. 2. The weekly number of dengue cases per 1000 individuals during the 2002 dengue epidemic diagnosed at the hospitals of the Mexican Institute of Public Health (IMSS) in each of the 10 municipalities in which the state of Colima, Mexico is divided (see Fig. 1).

(public) hospitals in the state of Colima provide service to 60% of the state population and are distributed across the state. Each dengue case is "naturally" assigned to one of the 10 municipalities using each patient's household address. Patients are classified according to the WHO case definition [43] as probable dengue cases whenever fever is present and as long as two or more of the following symptoms are also detected: myalgia, arthralgia, retro-orbital pain, headache, rash, or some hemorrhagic manifestations (e.g., petechiae, hematuria, hematemesis, melena). The index (reported) case was a 10-year old female diagnosed in the municipality of Manzanillo on January 11, 2002 (Fig. 2). The mean monthly temperature in the region was used to estimate the extrinsic mosquito incubation period using the thermodynamic relationship given in Focks et al. [24]. Local meteorological offices located in 9 of 10 municipalities provide temperature data.

A Dengue serotype 2 epidemic subsequent to a serotype 1, 3 or 4 epidemic leads to a higher incidence of Dengue hemorrhagic fever [49], making identification of the epidemic time course less prone to problems of underreporting or late detection. Consequently, the data from Colima are unlikely to have serious problems with under-reporting.

2.3. Method I

A standard epidemic model with fixed incubation periods in both hosts and vectors and an exponentially distributed infectious period in hosts is used to estimate the reproduction number [1]. We use a formula for the reproduction number that is based on the assumption that the initial epidemic growth phase is exponential.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

2.3.1. Standard dengue epidemic model

The transmission dynamics of dengue are modeled as in Anderson and May [1,20]. This model is an adaptation of the model proposed by Ross [46], or the extension by Macdonald [35]. This model has been used previously to estimate the reproduction number of dengue fever (e.g., [36,37,34,20]). The model classifies hosts (humans) in three epidemiological states: susceptible (S_h), incubating or exposed (E_h), infectious (I_h), and recovered (R_h). Female mosquitoes are classified as susceptible (S_v), incubating or exposed (E_v), and infectious (I_v). The total numbers of susceptible humans and adult susceptible mosquitoes are given by N_h and N_v, respectively. The disease-induced mortality rate on humans is assumed negligible while the birth and natural death rates of mosquitoes are assumed to have a common value μ_v. A susceptible human may be infected with dengue from the bite of an infectious mosquito during probing and feeding. The rate of susceptible host infection is $\lambda_v(t) = mC\beta_{hv}\frac{I_v(t)}{N_v(t)}$ where m is the number of female mosquitoes per person, C is the mean rate of mosquito bites per mosquito, β_{hv} is a constant transmission probability per bite from an infectious mosquito, and $\frac{I_v(t)}{N_v(t)}$ is the probability that a mosquito bite is made by an infectious mosquito. Humans infected with dengue undergo an incubation period assumed to be of fixed length τ_i followed by an infectious period of mean duration $1/\gamma_h$. Susceptible mosquitoes become infected from an infectious human during probing and feeding at the rate $\lambda_h(t) = C\beta_{vh}\frac{I_h(t)}{N_h(t)}$ where β_{vh} is a constant transmission probability per bite from an infectious human to a susceptible mosquito, and $\frac{I_h(t)}{N_h(t)}$ is the probability that a random mosquito bite is made to an infectious human at time t. Furthermore, infected mosquitoes experience an (assumed) fixed extrinsic incubation period τ_e (ambient temperature dependent following the relation of Focks et al. [24]) that is followed by an infectious state from which vectors do not recover. Their mean adult lifespan is $1/\mu_v$. The system of differential equations that describes the transmission dynamics of dengue under the above assumptions is given by the non-linear system of delay differential equations:

$$\begin{cases} \dot{S}_h(t) &= -\lambda_v(t)S_h(t) \\ \dot{I}_h(t) &= \lambda_v(t-\tau_i)S_h(t-\tau_i) - \gamma_h I_h(t) \\ \dot{R}_h(t) &= \gamma_h I_h(t) \\ \dot{S}_v(t) &= \mu_v N_v(t) - \lambda_h(t)S_v(t) - \mu_v S_v(t) \\ \dot{I}_v(t) &= e^{-\mu_v\tau_e}\lambda_h(t-\tau_e)S_v(t-\tau_e) - \mu_v I_v(t) \end{cases} \quad (1)$$

where the dot denotes time derivatives. For model 1, the basic reproduction number (see [1]) is given by:

$$\mathcal{R}_0 = \frac{mC^2\beta_{vh}\beta_{hv}}{\mu_v\gamma_h}e^{-\mu_v\tau_e} \quad (2)$$

$\mathcal{R}_0$ is the product of the number of infectious mosquitoes generated during the infectious period of a primary infectious human ($\frac{mC\beta_{vh}}{\gamma_h}$) and the number of infectious humans generated by the proportion of infectious mosquitoes surviving the extrinsic incubation period ($\frac{C\beta_{hv}e^{-\mu_v\tau_e}}{\mu_v}$). For the case of vector-borne diseases, a different definition of the reproduction number can be given in terms of the number of secondary cases generated either in humans or vectors, which is typically obtained from the next generation method [14,4,6]. We use the "classical" definition of transmissibility in

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

terms of the mean number of secondary infectious cases (humans) generated by a primary infectious human [1] to facilitate comparisons of our estimates with past published results.

2.3.2. Estimating $\mathcal{R}_p$ from the intrinsic growth rate

The basic reproduction number is most often estimated from data in the early epidemic phase, that is, prior to the introduction of mitigative interventions including behavioral changes, and at a time when the effects of susceptible depletion are negligible. Favier et al. [20] derived an approximation to Formula 2 of the basic reproduction number of Model 1 that assumes exponential initial epidemic growth. This formula includes the initial growth rate of the epidemic (r), two parameters related to the host epidemiology (τ_i and γ_h), and two entomological parameters (τ_e, μ_v). Their expression is

$$\mathcal{R}_0 = \left(1 + \frac{r}{\gamma_h}\right)\left(1 + \frac{r}{\mu_v}\right)e^{r(\tau_e+\tau_i)} \tag{3}$$

where r, the initial rate of epidemic growth, is tied in to the dominant eigenvalue of the linearization around the infection-free state of Model 1. Reporting rates typically vary considerably over the course of an epidemic. However, as discussed by Favier et al. [20], their estimation method is robust to the type of underreporting that is generated by asymptomatic or mild cases of dengue as long as the reporting rate is "constant" during the initial epidemic growth phase and across reporting units (e.g., hospitals).

From the time series epidemic data, we estimate the initial intrinsic epidemic growth rate r assuming an exponential-growth phase. The assumed initial exponential phase of the epidemic corresponds to the "free course" state of the epidemic in the absence of control interventions, behavioral changes, and saturation effects. During the 2002 epidemic in Colima, intervention that targeted the vector (malathion spraying) were put in place but late in the epidemic. The cumulative number of dengue cases (y_t, $t = 1, 2, \ldots, n$) were fitted using the simple exponential function $\hat{y}_t = b_0 e^{rt}$. The range, t_n, was at least 10 weeks long and bounded above when the χ^2 goodness-of-fit statistic reached a minimum (Fig. 3) [20].

2.3.3. Uncertainty analysis on $\mathcal{R}_p$

We assess the uncertainty in the reproduction number estimates that result from the variability in the input parameters: r, τ_i, γ_h, τ_e, and μ_v [2,7,34]. This uncertainty in the reproduction number is estimated by independently sampling parameter values (10^5 samples) from appropriate probability density functions [7]. Values for the initial epidemic growth rate r come from the sampling of a normal distribution with the appropriate mean and variance. Sampled values for the human incubation period τ_i come from a Gamma distribution with mean 5.5 days (95% CI: 4, 7) [26], and the infectiousness period ($1/\gamma_h$) values come from a Gamma distribution with mean 5 days (95% CI: 3, 7) [26]. The extrinsic incubation period is assumed to vary with the mean temperature according to the relation given in Focks et al. [24]. For each municipality, we estimate a mean temperature using the monthly temperature measures during the exponential phase of the epidemic. The estimated mean temperatures (Table 1) are above the minimal hatching temperatures for mosquito eggs (varying from 20 to 13 °C) obtained from experimental studies [11]. The mosquito mortality rate is assumed to be independent of ambient temperature as in other studies [45] and sampled from a Gamma distribution with a mean of 10.5 days (95% CI: 6, 15), which is consistent with known field study [40]. Parameter definitions and distributions are summarized in Table 2.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

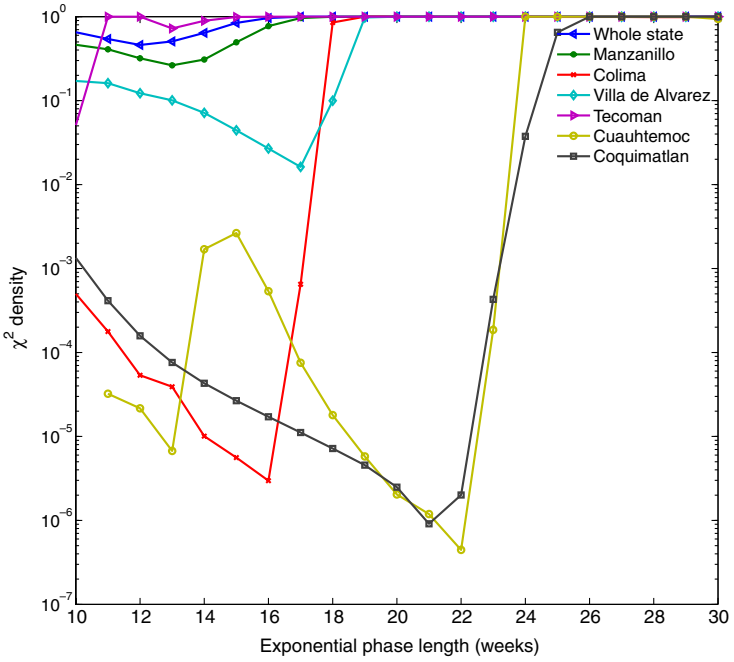

Fig. 3. The χ^2 density of the goodness of fit provided by the exponential function (Method I) to the initial epidemic growth phase of the cumulative number dengue cases comprising at least 10 epidemic weeks. The exponential phase length of the epidemics is chosen to minimize the χ^2 density. For example, using the χ^2 density goodness of fit criterion, the exponential phase for the whole state epidemic data is predicted to last 12 weeks.

Table 1
Estimates of the population size (N), total number of dengue notifications, mean temperature, and the extrinsic incubation period (τ_e) for the aggregated state data and for each of the 6 Colima municipalities that experienced the largest epidemic sizes

Municipality	N	Total dengue	Mean temperature (95% CI) °C	τ_e (95% CI) days
Whole state	488,028	4040	24.21 (20.28,28.14)	12.97 (9.25,18.87)
Manzanillo	108,584	1334	22.10 (21.22,22.98)	15.56 (14.44,17.40)
Colima	120,781	1167	25.55 (22.64,28.46)	11.11 (9.25,14.44)
Villa de Alvarez	66,300	891	24.98 (21.39,28.57)	11.86 (8.51,17.40)
Tecoman	91,036	338	25.83 (23.43,28.22)	11.11 (9.25,14.44)
Cuauhtemoc	25,462	114	23.97 (21.67,26.27)	12.97 (11.11,15.56)
Coquimatlan	16,939	94	25.88 (23.56,28.19)	11.11 (9.25,12.97)

The extrinsic incubation period was estimated using the local monthly temperature during the initial epidemic phase as determined by the goodness-of-fit statistic [20] and following the thermodynamic relation from Focks et al. [24] to fix the temperature dependence on the mosquito incubation time [24].

2.4. Method II

This method differs from Method I in two aspects: (1) The incubation period distributions in both hosts and vectors as well as the infectious period in hosts are modeled using a

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

Table 2
Model parameter definitions and their corresponding baseline distributions used in the estimation of the reproduction number from Method I

Parameter	Definition	Mean (95% CI)	Source	Probability distribution
r	Initial epidemic growth rate	Table 2	Estimated	Normal
τ_i	Mean intrinsic incubation period	5.5 (4,7) days	[26]	Gamma(53.8, 0.1)
$1/\gamma_h$	Mean host infectious period	5.0 (3,7) days	[26]	Gamma(25, 0.2)
$1/\mu_v$	Mean adult mosquito lifespan	10.5 (6,15) days	[40]	Gamma(21.8, 0.48)
τ_e	Mean extrinsic incubation period	Table 2	[24]	Gamma

Each parameter is sampled from their corresponding probability density function via simple random sampling to generate 10^5 sets of parameter values.

stage-progression model and (2) the best model trajectory is directly fitted to the epidemic data using least-square fitting techniques. That is, it does not assume an initial exponential epidemic growth phase.

2.4.1. Epidemic model incorporating more realistic incubation and infectious period distributions

We relax the assumption of fixed incubation periods and the exponentially distributed infectious period in humans of the baseline dengue Model (1) via the use of a stage-progression model, or the so-called linear chain trick [29,28,50]. The incubation and infectious periods are modeled as the progression in e_h incubation substates in humans $(E_{h_1}, E_{h_2}, \ldots, E_{h_{e_h}})$, e_v incubation substates in mosquitoes $(E_{v_1}, E_{v_2}, \ldots, E_{v_{e_v}})$ and i_h infectious substates in humans $(I_{h_1}, I_{h_2}, \ldots, I_{h_{i_h}})$. Under this formulation, the resulting incubation and infectious periods follow a gamma distribution with integer parameters e_h, e_v and i_h, respectively. When the rates of progression between substates are given by $e_h k_h$, $e_v k_v$ for the incubation periods and $i_h \gamma_h$ for the infectious period in humans, the resulting gamma distribution has means $1/k_v$, $1/k_h$ and $1/\gamma_h$ for the incubation and infectious periods, respectively, and the corresponding variances are given by $1/(e_h k_h^2)$, $1/(e_v k_v^2)$ and $1/(i_h \gamma_h^2)$, respectively. Incorporating this stage-progression in the intrinsic and extrinsic incubation periods and in the infectious period in humans into a system of differential equations gives:

$$
\begin{cases}
\dot{S_h}(t) &= -\lambda_v(t) S_h(t) \\
\dot{E_{h_1}}(t) &= \lambda_v(t) S_h(t) - k_h e_h E_{h_1}(t) \\
\dot{E_{h_j}}(t) &= k_h e_h E_{h_{j-1}}(t) - k_h e_h E_{h_j}(t), \ 2 \leqslant j \leqslant e_h \\
\dot{I_{h_1}}(t) &= k_h e_h E_{h_{e_h}}(t) - \gamma_h i_h I_{h_1}(t) \\
\dot{I_{h_j}}(t) &= \gamma_h i_h I_{h_{j-1}}(t) - \gamma_h i_h I_{h_j}(t), \ 2 \leqslant j \leqslant i_h \\
\dot{C}(t) &= k_h e_h E_{h_{e_h}}(t) \\
\dot{R_h}(t) &= \gamma_h i_h I_{h_{i_h}}(t) \\
\dot{S_v}(t) &= \mu_v N_v(t) - \lambda_h(t) S_v(t) - \mu_v S_v(t) \\
\dot{E_{v_1}}(t) &= \lambda_h(t) S_v(t) - (k_v e_v + \mu_v) E_{v_1}(t) \\
\dot{E_{v_j}}(t) &= k_v e_v E_{v_{j-1}}(t) - (k_v e_v + \mu_v) E_{v_j}(t), \ 2 \leqslant j \leqslant e_v \\
\dot{I_v}(t) &= k_v e_v E_{v_{e_v}}(t) - \mu_v I_v(t)
\end{cases}
\tag{4}
$$

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

where $C(t)$ is the cumulative number of dengue cases. The total human population size is given by $N_h(t) = S_h(t) + \sum_{j=1}^{e_h} E_{h_j}(t) + \sum_{j=1}^{i_h} I_{h_j}(t) + R_h(t)$, and the total mosquito population size is given by $N_v(t) = S_v(t) + \sum_{j=1}^{e_v} E_{v_j}(t) + I_v(t)$. Moreover, the forces of infection for humans and mosquitoes are given by $\lambda_h(t) = C\beta_{vh} \frac{\sum_{j=1}^{i_h} I_{h_j}(t)}{N_h(t)}$ and $\lambda_v(t) = mC\beta_{hv} \frac{I_v(t)}{N_v(t)}$, respectively.

The basic reproduction number for model 4 is given by the formula:

$$\mathcal{R}_0 = \frac{mC^2\beta_{vh}\beta_{hv}}{\mu_v\gamma_h}\left(\frac{e_v k_v}{e_v k_v + \mu_v}\right)^{e_v} \tag{5}$$

$\mathcal{R}_0$ expressions for models 1 and 4 differ in the factor expressing the proportion of infectious mosquitoes surviving the extrinsic incubation period. In fact, the reproduction number of Model 4 converges to that of Model 1 as $e_v \to \infty$. Fig. 4 shows a representative example of the effects of the number of substates that model the extrinsic incubation period (e_v) on the reproduction number, the final epidemic size, and the epidemic peak size. Moreover, the effect of the shape of the incubation period distributions on the shape of the epidemic growth phase is illustrated in Fig. 5.

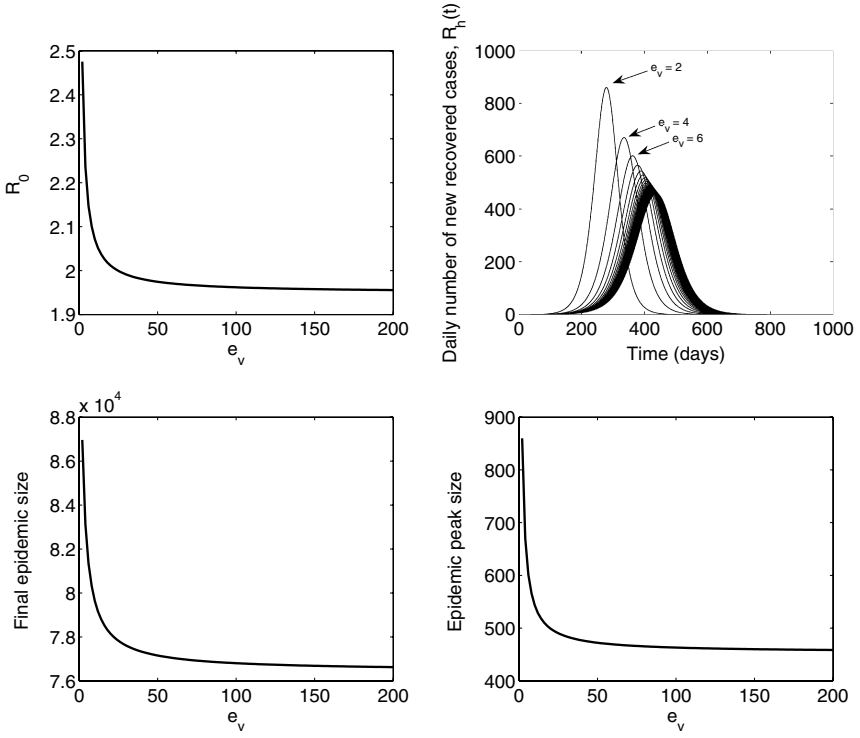

Fig. 4. The effects of the number of substates modeling the extrinsic incubation period ($e_v = 2,4,6,\ldots,200$) using the stage-progression model 4 on the reproduction number, the final epidemic size, and the epidemic peak size. For this representative example, parameter values were set as follows: $m = 3$ female mosquitoes per human, $C\beta_{vh} = C\beta_{hv} = 0.197$ bites per mosquito per day, $\mu_v = 1/10.5$ days^{-1}, $k_m = 1/12$ days^{-1}, $k_h = 1/5.5$ days^{-1}, $\gamma_h = 1/5$ days^{-1}, $N_h(0) = 10000$ humans, $I_h(0) = 1$ humans, $I_v(0) = 1$ mosquitoes.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

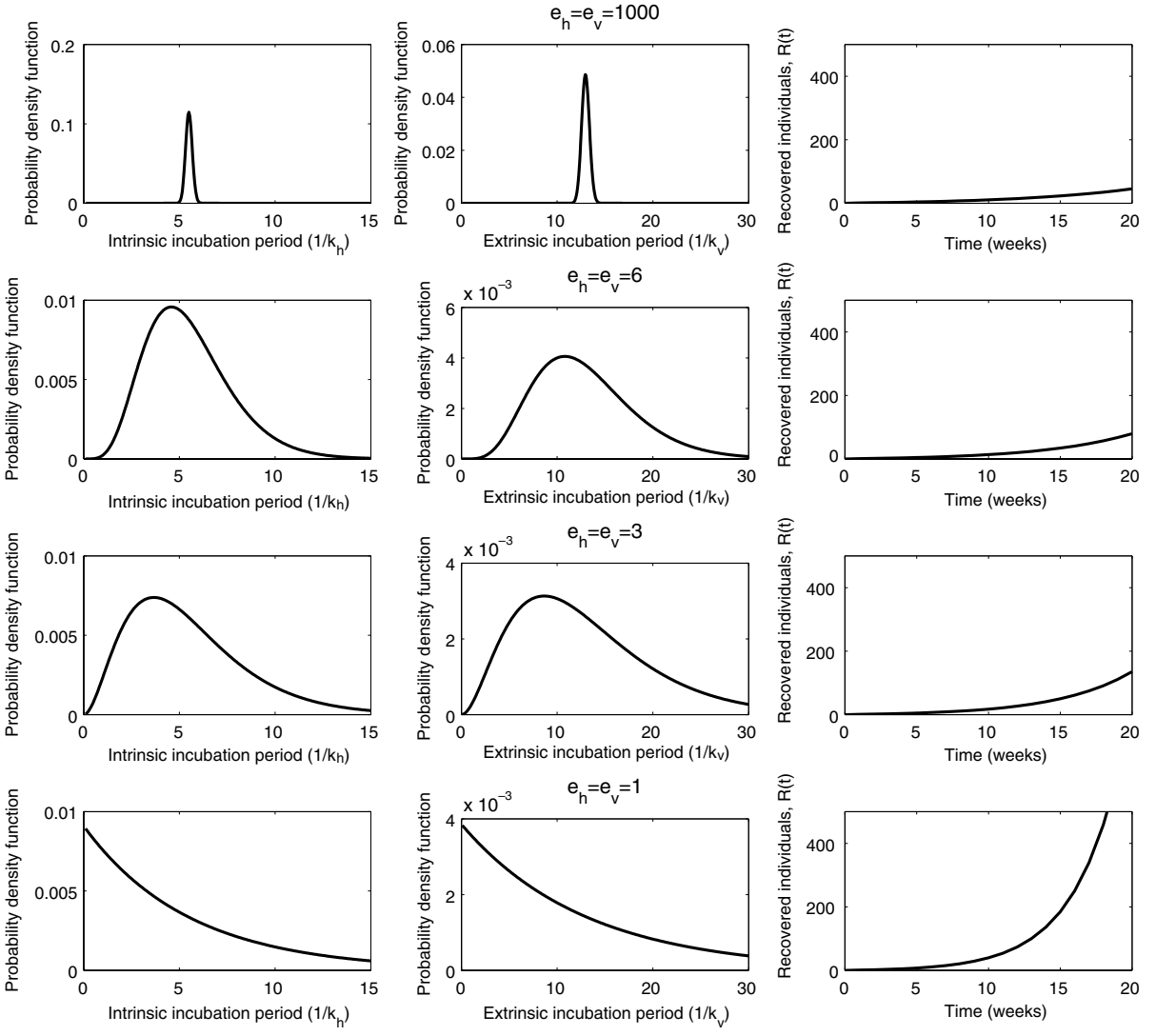

Fig. 5. The effect of the shape of the incubation period distributions (in hosts and vectors) on the shape of the epidemic growth phase. For illustration we use $e_h = e_v = 1, 3, 6, 1000$ in the stage-progression model 4, and the incubation period distributions are well approximated by gamma distributions with the appropriate shape and scale parameters. Other parameter values were set as follows: $m = 3$ female mosquitoes per human, $C\beta_{vh} = C\beta_{hv} = 0.197$ bites per mosquito per day, $\mu_v = 1/10.5$ days^{-1}, $k_m = 1/13$ days^{-1}, $k_h = 1/5.5$ days^{-1}, $\gamma_h = 1/5$ days^{-1}, $N_h(0) = 100{,}000$ humans, $I_h(0) = 1$ humans, $I_v(0) = 1$ mosquitoes.

2.4.2. Estimating $\mathcal{R}_p$ via model fitting to epidemic data

In order to estimate $C\beta_v$, $C\beta_h$, the initial number of infectious hosts $(I_{h_1}(0))$, and the initial number of infectious vectors $(I_v(0))$, we fit the cumulative number of cases given by equation $C(t)$ to the initial phase of the cumulative number of dengue cases that is bounded above when the χ^2 goodness-of-fit statistic reaches a minimum [20]. We implemented a least-square fitting

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

procedure in MATLAB (The Mathworks, Inc.) using the built-in routine `lsqcurvefit` in the optimization toolbox. Because of lack of reliable estimates for the mean ratio of female mosquitoes per host (m), we fixed $m = 3$ and performed a sensitivity analysis on the estimates of the reproduction number to changes in parameter m. The mean mosquito mortality rate (μ), the mean extrinsic and intrinsic incubation periods ($1/k_v$ and $1/k_h$), the mean infectious period ($1\gamma_h$), and the local population size were taken from published literature and are given in Tables 1 and 2.

We estimate the number of stages necessary to model more realistic incubation and infectious distributions based on the approximate mean and variance of the distributions of the intrinsic ($1/k_h = 5.5$ days,$\sigma^2_{k_h} = 0.75^2$ days^2) and extrinsic ($1/k_v = 12.97$ days,$\sigma^2_{k_v} = 2.41^2$ days^2) (for the entire state) incubation periods and the infectious period in humans ($1/\gamma_h = 5.0$ days,$\sigma^2_{\gamma_h} = 1$ days^2) (Tables 1 and 2). The number of compartments necessary to model the incubation periods are $e_h = 1/(k_h^2\sigma^2_{k_h}) \approx 54$ and $e_v = 1/(k_v^2\sigma^2_{k_v}) \approx 29$ (for the entire state), and $i_h = 1/(\gamma_h^2\sigma^2_{\gamma_h}) \approx 25$ for the infectious period in humans.

2.4.3. Uncertainty analysis on $\mathcal{R}_p$

We generate uncertainty bounds on $\mathcal{R}_p$ by assuming an observation error structure for the epidemic timeseries. We construct 95% confidence intervals for $\mathcal{R}_p$ via the parametric bootstrap [16] using a set of realizations of the best-fit curve $C(t)$. Each realization of the cumulative number of case notifications $C_i(t)$ ($i = 1, 2, \ldots, m$) is generated as follows: for each observation $C(t)$ for $t = 2, 3, \ldots, n$ weeks, generate a new observation $C'_i(t)$ for $t \geqslant 2$ ($C'_i(1) = C(1)$) that is sampled from a Poisson distribution with mean: $C(t) - C(t-1)$ (the weekly increment in $C(t)$ from week $t-1$ to week t). The corresponding realization of the cumulative number of cases is given by $C_i(t) = \sum_{j=1}^{t} C'_i(t)$ where $t = 1, 2, 3, \ldots, n$. The reproduction number was then estimated from each of 200 simulated epidemic curves, and the distribution of estimated reproduction numbers can be used to construct 95% confidence intervals. These confidence intervals should be interpreted as containing 95% of future estimates when the same assumptions are made and the only noise source is observation error [5].

3. Results

3.1. Estimates of the reproduction number $\mathcal{R}_p$

The mean extrinsic incubation period is shortest for the municipalities of Tecoman and Coquimatlan (11.1 days) and largest for the municipality of Manzanillo (15.6 days) following Focks et al. [24]. The mean initial growth rate (r) ranges from 0.05 (1/week) (Coquimatlan) to 0.33 (1/week) (Tecoman). Using Method I, we estimate an overall mean reproduction number of 3.09 (SD 0.37) using the aggregated epidemic data of the 2002 dengue epidemic for the whole state of Colima, Mexico. The reproduction number for the six municipalities that experienced the largest epidemic size ranges from 1.24 (SD 0.05) for the municipality of Coquimatlan to 4.22 (SD 0.66) for the municipality of Tecoman. On the other hand, using the refined Method II, we obtained systematically and significantly lower estimates of the reproduction number than those obtained using Method I (Table 3). Using Method II, the overall mean reproduction number

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

Table 3
Estimates of the reproduction number, the number of epidemic weeks of the cumulative number of dengue notifications (t^*) used in the estimation, and other related parameters obtained from the two different methods as explained in the text

Municipality	Method I			Method II					
	t^* wks	r (95% CI) per wk	$\mathcal{R}_p$ (95% CI)	$C\beta_v$	$C\beta_h$	$I_v(0)$	$I_{h_1}(0)$	t^* wks	$\mathcal{R}_p$ (95% CI)
Whole state	12	0.25 (0.22, 0.27)	3.09 (2.34, 3.84)	1.46	0.04	4.68	64.60	16	2.0 (1.75, 2.23)
Manzanillo	13	0.24 (0.22, 0.26)	3.26 (2.70, 3.82)	0.81	0.08	5.89	17.66	16	2.30 (2.00, 2.59)
Colima	16	0.14 (0.12, 0.15)	1.84 (1.62, 2.06)	1.36	0.01	1.58	7.34	14	1.08 (0.46, 1.70)
Villa de Alvarez	17	0.12 (0.09, 0.14)	1.67 (1.46, 1.89)	0.36	0.06	0.99	2.84	17	1.07 (0.45, 1.70)
Tecoman	10	0.33 (0.27, 0.39)	4.22 (2.90, 5.54)	0.63	0.09	1.20	0.93	13	3.30 (1.63, 4.97)
Cuauhtemoc	22	0.11 (0.09, 0.13)	1.64 (1.44, 1.83)	2.68	0.004	0.68	5.16	13	0.54 (0.0, 1.48)
Coquimatlan	21	0.05 (0.04, 0.06)	1.24 (1.15, 1.33)	2.64	0.003	1.64	17.14	19	0.49 (0.0, 0.99)

For Method I, the number of degrees of freedom (df) is given by df $= t^*$ (number of data points), -2 (number of fitting parameters) whereas for Method II, df $= t^*$ (number of data points) -4 (number of fitting parameters).

$\mathcal{R}_p = 2.0$ (SD 0.12) and local $\mathcal{R}_p$ estimates range from 0.49 (SD 0.25) for the municipality of Coquimatlan to 3.30 (SD 0.84) for the municipality of Tecoman. The best fits provided by model (4) were in good agreement with the epidemic data (Fig. 6). Estimates of the reproduction number did not change significantly when parameter m was fixed to 1, 3, or 6 although changes occurred in the individual parameter estimates of quantities $C\beta_v$, $C\beta_h$, $I_{h_1}(0)$, and $I_v(0)$.

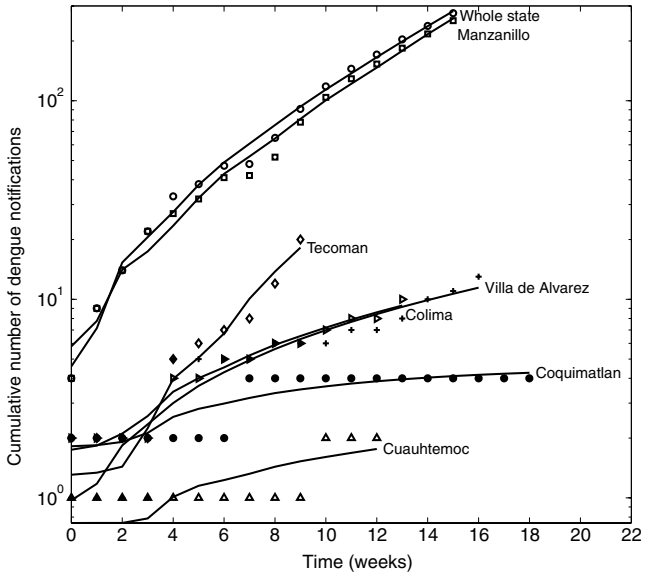

Fig. 6. The best fits (solid lines) provided by the stage progression model (Method II) to the initial epidemic phase of the state-wide and local dengue epidemics (circles) in logarithmic scale. The duration of the initial epidemic phase was determined by the χ^2 goodness-of-fit statistic [20] as in Method I.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

3.2. Epidemic onset, peak and size

The week of epidemic onset (in the 10 different Colima municipalities) ranged from week 2 to 26, in the year 2002. The mean epidemic week of onset was week 12 (SD 8.4). Epidemic week peaks occurred between week 24 and 35. We found a statistically significant correlation between the epidemic peak-time and epidemic size ($\rho = 0.92$, P-value $= 0.0002$), and a negative correlation between *onset week* and epidemic size but without achieving statistical significance ($\rho = -0.62$, P-value $= 0.057$). The weeks of epidemic onset were found to be negatively correlated with the epidemic *peak-sizes* (borderline significant) in the different municipalities ($\rho = -0.56$, P-value $= 0.095$) but no correlation was found with the *peak-times* ($\rho = -0.03$, P-value $= 0.93$).

The final local epidemic sizes scale linearly with the local population sizes. A linear fit to the final number of dengue notifications per municipality as a function of their corresponding population size was found to be statistically significant (P-value $= 0.0003$) and explained 81.0% of the observed variance (MSE $= 58032$) (Fig. 7). This observation supports our assumption of a

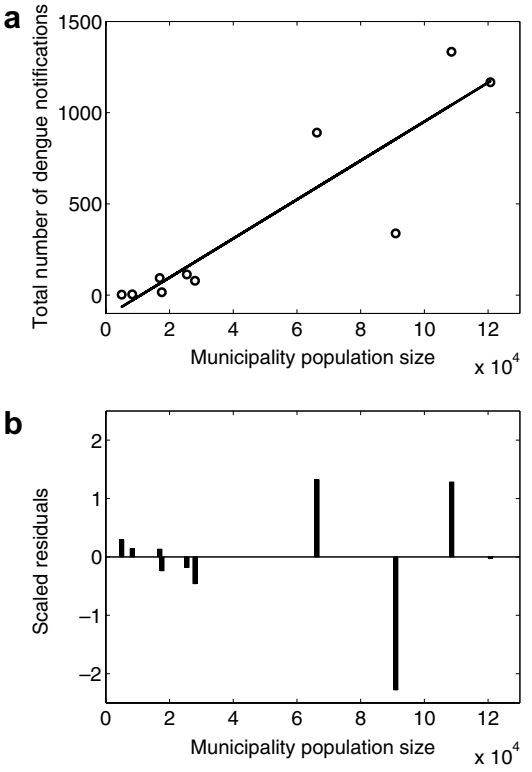

Fig. 7. The total number of dengue notifications in each of the municipalities of the State of Colima, Mexico during the 2002 epidemic as a function of the population size per municipality. (a) The circles are the data for the 10 municipalities, and the solid line is the regression model: `Total dengue notifications` $= -117.25 + 0.0107$ `(local population size)` with a coefficient of determination of 81.0% and P-value < 0.001. (b) The scaled residuals fall approximately within ± 2 standard deviations.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

roughly constant number of female mosquitoes per human across urban and rural regions. This linear model is given by:

$$\texttt{Total dengue notifications} = -117.25 + 0.0107\ (\texttt{local population size}) \quad (6)$$

4. Discussion

We have carried out a retrospective analysis of the 2002 dengue epidemic in the state of Colima, Mexico that included the estimation of the overall and local reproduction numbers using two different methods. The first method uses a standard model described by Anderson and May [1] for the transmission dynamics of malaria with fixed incubation periods in both hosts and vectors and an exponentially distributed infectious period in hosts (recently used to estimate the reproduction number of dengue epidemics in several Brazilian regions [36,37,34,20]) and assumes an initial exponential epidemic growth phase. On the other hand, the second method uses an epidemic model that incorporates more realistic incubation and infectious period distributions and estimates the reproduction number via trajectory matching to the epidemic timeseries. We also used the thermodynamic relation from Focks et al. [24] to fix the temperature dependence on the mosquito incubation time [24]. Our results indicate a significant bias in the estimates of the reproduction number obtained from Method I relative to those obtained from the refined Method II. Specifically, the reproduction number is overestimated when using Method I relative to Method II. Therefore, estimates of the reproduction number obtained using Method I may overestimate the intensity of interventions and associated costs for epidemic control. Estimates of the reproduction number obtained from Method I are affected by two sources of bias: (1) Formula (3) of the reproduction number used in Method I was derived under the assumption of a pure exponential growth phase during the epidemic take-off and (2) the mathematical Model (1) used in Method I makes the extreme assumptions of fixed incubation periods in hosts and vectors and the exponentially distributed infectious period in hosts.

While the pure exponential initial growth assumption was a good approximation to estimate the reproduction number (Method I) from the state-wide epidemic data and from some local epidemics (i.e., Manzanillo, Colima, Villa de Alvarez, Tecoman), such an assumption was clearly not adequate to estimate the reproduction number for the local dengue outbreaks in Cuauhtemoc and Coquimatlan (Fig. 6). Consequently, Method I estimated the reproduction number to be above one for the municipalities of Cuauhtemoc and Coquimatlan when these reproduction numbers are clearly below this threshold when more precisely estimated by Method II (Table 3 and Fig. 6). In fact, the pure exponential growth assumption in Method I provided a larger source of bias than that associated to the extreme assumptions on the distribution of the epidemiological parameters in model (1). For example, by fitting Model (1) directly to the dengue epidemic curves instead of relying on the initial intrinsic growth rate (r), we estimate a mean reproduction number of 2.1 from the state-wide epidemic data and a mean reproduction number of 2.4 for the municipality of Manzanillo compared to the mean reproduction numbers of 2.0 and 2.3, respectively, obtained using Method II for the same epidemic data.

Using Method II, we have estimated an overall reproduction number ($\mathcal{R}_p$) of 2.0 (95% CI: 1.75, 2.23) using the aggregated, state-wide, data and the mean ambient temperature from each of 9

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

meteorological stations and a thermodynamic temperature dependence of mosquito incubation times [24,34]. The reproduction number was lowest in the municipality of Coquimatlan [0.49 (0.0, 0.99)] and largest in the municipality of Tecoman [3.30 (1.63, 4.97)]. A single control strategy based on the state-wide reproduction number overestimates the level of mitigation required in some municipalities and underestimate in others [9]. Nevertheless, local $\mathcal{R}_p$ estimates need to be interpreted with caution since these were estimated considering the different municipalities to be disconnected (i.e., no host mobility between municipalities). While we cannot determine the smallest scale of heterogeneity in $\mathcal{R}_p$ from these data, it is no larger than the municipalities.

Because candidate dengue vaccines are still in testing or development, public health controls must rely on reducing the reproduction number via the elimination of vectors, shortening the mean vector lifespan (parameters m and $1/\mu_v$, respectively) or directly reducing the mosquito biting rate in humans through, for example, netting, screens, application of insecticides to clothing or the application of mosquito repellents. Vector control programs include the removal of breeding sites generated by humans in households (e.g., old toys, water containers, and tires), larvicidal control including ovitraps [42], and malathion spraying to target adult mosquito populations.

Estimates of the reproduction number for dengue fever are somewhat sparse, and large reproduction numbers reported in a few papers raise the possibility of strong locale-dependent variations in $\mathcal{R}_p$, consistent with picture of strong locale-variation seen in Colima. Koopman et al. [31] estimate the reproduction number using the relationship between the basic reproduction number and the final epidemic size from a national serosurvey comprising 3408 households in 70 localities in Mexico from March to October, 1986. Their mean estimate of the reproduction number is 1.3 (maximum of 2.4) significantly lower than the mean estimate reported here. Ferguson et al. [23] report estimates for dengue from cross-sectional serological data collected in Thailand using statistical methods. These researchers report a reproduction number in the range 4–6 for dengue Serotype 2 using a simple model with no interacting strains and constant force of infection. The reproduction number for dengue has also been estimated in the state of São Paulo, Brazil [36,37] and a number of Brazilian regions covering different tropical climates [20]. Marques et al. [36] estimated reproduction numbers in the range [1.6, 2.5] in 12 cities of the state of São Paulo, Brazil during a 1991 epidemic. During the 2000 epidemic in 12 cities of the state of São Paulo, Brazil, Massad et al. [37] estimated reproduction numbers in the range [3.6, 12.9]. More recently, Favier et al. [20] estimated a reproduction number that ranged widely from 2.0 to 103 for dengue epidemics occurring during the years 1996–2003 in 9 Brazilian regions. Variability in estimates of the reproduction number may be due to a combination of factors that include pathogen biology, improved public health surveillance, and better climatological conditions for the survival and effective transmission of the vectors. Depending on the severity of disease and the prevalence of diagnostic laboratory work, some data sets, particularly those including less severe disease may be significantly confounded by other diseases during the initial clinical phase, e.g. influenza, yellow fever, malaria. Whereas DSS has a unique pathophysiologic presentation in infectious disease, some cases of dengue fever are undifferentiated and exhibit mild febrile illness lasting 1–3 days.

We have observed a linear relationship between the final size of the epidemics in the different localities and their corresponding population size (Fig. 7). By comparison, we have previously reported (for the same region) a linear relationship between the total number of scorpion stings of humans (a type of vector-borne disease) and the population size for most municipalities of Colima except for the most urbanized municipalities of Colima and Villa de Alvarez (Fig. 1,

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

[8]). Hence, it seems reasonable to assume that the mean number of female mosquitoes per human is roughly constant across the state of Colima. Moreover, our findings indicate that the burden of dengue during the 2002 epidemic in the state of Colima, Mexico was not significantly affected by differences in urbanization levels across the state.

Acknowledgements

We thank an anonymous reviewer for providing useful comments that helped to improve our manuscript. This work was carried out under the auspices of the National Nuclear Security Administration of the US Department of Energy at Los Alamos National Laboratory under Contract No. DE-AC52-06NA25396 and was partially supported by the NNSA's Laboratory Directed Research and Development Program.

References

[1] R.M. Anderson, R.M. May, Infectious Diseases of Humans, Oxford University Press, Oxford, UK, 1991.
[2] S.M. Blower, H. Dowlatabadi, Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example, International Statistical Review 62 (2) (1994) 229–243.
[3] F. Brauer, C. Castillo-Chavez, Mathematical Models in Population Biology and Epidemiology, Springer Verlag, New York, 2000.
[4] C. Bowman, A.B. Gumel, P. van den Driessche, J. Wu, H. Zhu, A mathematical model for assessing control strategies against West Nile virus, Bulletin of Mathematical Biology 67 (2005) 1107–1133.
[5] T.L. Burr, G. Chowell, Observation and model error effects on parameter estimates in susceptible-infected-recovered epidemic model, Far East Journal of Theoretical Statistics 19 (2006) 163–183.
[6] N. Chitnis, J.M. Cushing, J.M. Hyman, Bifurcation analysis of a mathematical model for malaria transmission, SIAM Journal of Applied Mathematics 67 (2006) 24–45.
[7] G. Chowell, C. Castillo-Chavez, P.W. Fenimore, C. Kribs-Zaleta, L. Arriola, J.M. Hyman, Model parameters and outbreak control for SARS, Emerging Infectious Diseases 10 (2004) 1258–1263.
[8] G. Chowell, J.M. Hyman, P. Diaz-Dueñas, N.W. Hengartner, Predicting scorpion sting incidence in an endemic region using climatological variables, International Journal of Environmental Health Research 15 (2005) 425–435.
[9] G. Chowell, A.L. Rivas, S.D. Smith, J.M. Hyman, Identification of case clusters and counties of greater infective connectivity in the 2001 uruguayan foot-and-mouth disease epidemic, American Journal of Veterinary Research 67 (2006) 1–12.
[10] G. Chowell, F. Sanchez, Climate-based descriptive models of dengue fever, Journal of Environmental Health 68 (2006) 60–63.
[11] R. Christophers, *Aedes aegypti* (L.), the Yellow Fever Mosquito, Cambridge University Press, Cambridge, 1960.
[12] D.A. Cummings, I.B. Schwartz, L. Billings, L.B. Shaw, D.S. Burke, Dynamic effects of antibody-dependent enhancement on the fitness of viruses, PNAS 102 (2005) 15259–15264.
[13] Instituto Nacional de Estadística Geografia e Informática. XII census of population and household, 2000, accessed March 10, 2005. Available from: http://www.inegi.gob.mx/inegi/default.asp.
[14] O. Diekmann, J. Heesterbeek, Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation, Wiley, New York, 2000.
[15] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Mathematical Biosciences 180 (2002) 29–48.
[16] B. Efron, R. Tibshirani, Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy, Statistical Science 1 (1986) 54–75.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

[17] F. Espinoza-Gómez, C.M. Hernández-Suarez, R. Coll-Cardenas, Factores que modifican los indices larvarios de Aedes aegypti en Colima, Mexico [factors that modify the larval indices of Aedes aegypti in Colima, Mexico], Pan American Journal of Public Health 10 (2001) 6–12.
[18] F. Espinoza-Gómez, C.M. Hernández-Suarez, R. Rendón-Ramrez, M.L. Carrillo-Alvarez, J.C. Flores-González, Transmisión interepidémica del dengue en la ciudad de Colima, Mexico [interepidemic transmission of dengue in the city of Colima, Mexico], Salud Publica Mexico 45 (2003) 365–370.
[19] L. Esteva, C. Vargas, Coexistence of different serotypes of dengue virus, Journal of Mathematical Biology 46 (2003) 31–47.
[20] C. Favier, N. Degallier, M.G. Rosa-Freitas, J.P. Boulanger, J.R. Costa Lima, J.F. Luitgards-Moura, C.E. Menkes, B. Mondet, C. Oliveira, E.T. Weimann, P. Tsouris, Early determination of the reproduction number for vector-borne diseases: the case of dengue in Brazil, Tropical Medicine and International Health 11 (2006) 332–340.
[21] C. Favier, D. Schmit, C.D. Muller-Graf, B. Cazelles, N. Degallier, B. Mondet, M.A. Dubois, Influence of spatial heterogeneity on an emerging infectious disease: the case of dengue epidemics, Proceedings Biological Sciences 272 (2005) 1171–1177.
[22] Z. Feng, X. Velasco-Hernandez, Competitive exclusion in a vector-host model for the dengue fever, Journal of Mathematical Biology 35 (1997) 523–544.
[23] N.M. Ferguson, C.A. Donnelly, R.M. Anderson, Transmission dynamics and epidemiology of dengue: insights from age-stratified sero-prevalence surveys, Philosophical Transactions of the Royal Society of London B 354 (1999) 757–768.
[24] D.A. Focks, E. Daniels, D.G. Haile, J.E. Keesling, A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results, American Journal of Tropical Medicine and Hygiene 53 (1995) 489–506.
[25] Mexican National Center for Epidemiological Surveillance and Disease Control (CENAVE). Dengue Serotypes Circulating in Mexico, accessed March 04, 2006. Available from: http://www.cenave.gob.mx/dengue/default.asp?id=14.
[26] D.J. Gubler, Dengue and dengue hemorrhagic fever, Clinical Microbiology Reviews 11 (1998) 480–496.
[27] M.G. Gúzman, G. Kouri, Dengue and dengue hemorrhagic fever in the Americas: lessons and challenges, Journal of Clinical Virology 27 (2003) 1–13.
[28] J.M. Hyman, J. Li, E.A. Stanley, The differential infectivity and staged progression models for the transmission of HIV, Mathematical Biosciences 155 (1999) 77–109.
[29] J.A. Jacquez, Compartmental Analysis in Biology and Medicine, Michigan Thompson-Shore Inc., Michigan, 1996.
[30] T.H. Jetten, D.A. Focks, Potential changes in the distribution of dengue transmission under climate warming, American Journal Tropical Medicine and Hygiene 57 (1997) 285–297.
[31] J.S. Koopman, D.R. Prevots, M.A. Vaca Marin, H. Gomez Dantes, M.L. Zarate Aquino, I.M. Longini Jr., J. Sepulveda Amor, Determinants and predictors of dengue infection in Mexico, American Journal of Epidemiology 133 (1991) 1168–1178.
[32] C.F. Li, T.W. Lim, L.L. Han, R. Fang, Rainfall, abundance of *Aedes aegypti* and dengue infection in Selangor, Malaysia, Southeast Asian Journal of Tropical Medicine and Public Health 16 (1985) 560–568.
[33] M.A. Lorono-Pino, C.B. Cropp, J.A. Farfan, A.V. Vorndam, E.M. Rodriguez-Angulo, E.P. Rosado-Paredes, L.F. Flores-Flores, B.J. Beaty, D.J. Gubler, Common occurrence of concurrent infections by multiple dengue virus serotypes, American Journal of Tropical Medicine and Hygiene 61 (1999) 725–730.
[34] P.M. Luz, C.T. Codeco, E. Massad, C.J. Struchiner, Uncertainties regarding dengue modeling in Rio de Janeiro, Brazil, Memórias do Instituto Oswaldo Cruz 98 (2003) 871–878.
[35] G. MacDonald, The Epidemiology and Control of Malaria, chapter Epidemics, Oxford University Press, London, 1957, pp. 45–62.
[36] C.A. Marques, O.P. Forattini, E. Massad, The basic reproduction number for dengue fever in São Paulo state, Brazil: 1990–1991 epidemic, Transactions of the Royal Society of Tropical Medicine and Hygiene 88 (1994) 58–59.
[37] E. Massad, F.A. Coutinho, M.N. Burattini, L.F. Lopez, The risk of yellow fever in a dengue-infested area, Transactions of the Royal Society of Tropical Medicine and Hygiene 95 (2001) 370–374.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011

[38] Singapore Ministry of Health. The communicable disease surveillance in Singapore 2004, accessed May 04, 2006. Available from: http://www.moh.gov.sg/cmaweb/attachments/publication/36c375c79a8t/Vector-Borne_Diseases.pdf.
[39] D.T. Mourya, P. Yadav, A.C. Mishra, Effect of temperature stress on immature stages and susceptibility of *Aedes aegypti* mosquitoes to chikungunya virus, American Journal Tropical Medicine and Hygiene 70 (2004) 346–350.
[40] L.E. Muir, B.H. Kay, *Aedes aegypti* survival and dispersal estimated by mark–release–recapture in northern Australia, American Journal of Tropical Medicine and Hygiene 58 (1998) 277–282.
[41] J. Navarrete-Espinosa, H. Gomez-Dantes, J.G. Celis-Quintal, J.L. Vazquez-Martinez, Clinical profile of dengue hemorrhagic fever cases in Mexico, Salud Publica Mexico 47 (2005) 193–200.
[42] E.-E. Ooi, K.-T. Goh, D.J. Gubler, Dengue prevention and 35 years of vector control in Singapore, Emerging Infectious Diseases 12 (6) (2006) 887–893.
[43] World Health Organization. Clinical diagnosis of dengue, accessed April 04, 2006. Available from: http://www.who.int/csr/resources/publications/dengue/012-23.pdf.
[44] World Health Organization. Dengue and dengue hemorrhagic fever, accessed March 04, 2006. Available from: http://www.who.int/mediacentre/factsheets/fs117/en/.
[45] M. Otero, H.G. Solari, N. Schweigmann, A stochastic population dynamics model for *Aedes aegypti*: Formulation and application to a city with temperate climate, Bulletin of Mathematical Biology 68 (2006) 1945–1974.
[46] R. Ross, The Prevention of Malaria, John Murray, London, 1910.
[47] G.W. Schultz, Seasonal abundance of dengue vectors in Manila, Republic of the Philippines, Southeast Asian Journal of Tropical Medicine and Public Health 24 (1993) 369–375.
[48] D.L. Smith, J. Dushoff, F.E. Mckenzie, The risk of a mosquito-borne infection in a heterogeneous environment, PLoS Biology 2 (2004) 1957–1964.
[49] D.W. Vaughn, S. Green, S. Kalayanarooj, B.L. Innis, S. Nimmannitya, S. Suntayakorn, T.P. Endy, B. Raengsakulrach, A.L. Rothman, F.A. Ennis, A. Nisalak, Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity, Journal of Infectious Diseases 181 (2000) 2–9.
[50] H.J. Wearing, P. Rohani, M.J. Keeling, Appropriate models for the management of infectious diseases, PLoS Medicine 2 (2005) e174.
[51] H.J. Wearing, P. Rohani, Ecological and immunological determinants of dengue epidemics, PNAS 103 (2006) 11802–11807.

Please cite this article in press as: G. Chowell et al., Estimation of the reproduction number of dengue fever ..., Math. Biosci. (2007), doi:10.1016/j.mbs.2006.11.011